## **PREFACE**

This document is a NIAID protocol template. It is provided to investigators for developing NIAID-sponsored clinical trial protocols. Note that instructions and explanatory text are indicated by <u>italics</u> and should be replaced in your protocol document with appropriate protocol-specific text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template.

This template provides a general format applicable to all clinical trials evaluating Study Agent(s)/Intervention(s). Where specific examples are provided, they are often from the vaccine area.

Refer questions regarding use of this protocol template to the appropriate NIAID Division or Branch sponsoring this clinical trial.

# **TITLE**

#### **NIAID Protocol Number:**

## Sponsored by:

National Institute of Allergy and Infectious Diseases (NIAID)

NIAID Funding Mechanism: (e.g., grant #, contract #)

Pharmaceutical Support Provided by: (if applicable)

Other Identifying Numbers:

IND Sponsor: (if applicable)

**Principal Investigator/Protocol Chair:** 

**NIAID Medical Monitor:** 

**NIAID Protocol Champion** 

**Draft or Version Number:** 

## **Day Month Year**

(Write out the month and use international date format, e.g., 23 June 2005)

This template is adapted from the ICH guidance document E6 (Good Clinical Practices), Section 6.

## **Confidentiality Statement**

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from NIAID (or others, as applicable), unless it is necessary to obtain informed consent from potential study participants.

## **Statement of Compliance**

Provide a statement that the trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and the applicable regulatory requirements. Use the applicable regulations and requirements depending on study location and sponsor requirements. Examples of requirements that are potentially applicable include:

- U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 and 21 CFR including parts 50 and 56 concerning informed consent and IRB regulations, if under IND, 21 CFR 312).
- Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use as amended by Commission Directive 2005/28/EC.
- Completion of Human Participants Protection Training

Refer to:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp http://www.cancer.gov/clinicaltrials/learning/page3

NIAID Clinical Terms of Award

# Signature Page 1

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

The Lead Principal Investigator (Protocol Chair) should sign Signature Page 1. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal I	nvestigator:			
·		Print/Type		
Signed:			Date:	
_	Name/Title			

# Signature Page 2

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

The Investigator(s) of Record (signature(s) on 1572) from each participating clinical site should sign the Signature Page 2 as appropriate. This Signature Page 2 should be maintained at each site.

Investigat	or(s) of Record:			
J	.,	Print/Type		
Signed:			Date:	
_	Name/Title			
Additional	Investigators:			
	-	Print/Type		
Signed:		GAIVIT	Date:	
_	Name/Title			
Additional	Investigators:			
		Print/Type		
Signed:			Date:	
	Name/Title			

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#### List of Abbreviations

This list should be modified to include protocol-specific terms.

AE Adverse Event/Adverse Experience

CFR Code of Federal Regulations
CIB Clinical Investigator's Brochure

CIOMS Council for International Organizations of Medical Sciences

CONSORT Consolidated Standards of Reporting Trials

CRF Case Report Form

CRO Contract Research Organization

DCC Data Coordinating Center

DSMB Data and Safety Monitoring Board
DSMC Data and Safety Monitoring Committee

FDA Food and Drug Administration
FWA Federal-Wide Assurance
GCP Good Clinical Practice

HIPAA Health Insurance Portability and Accountability Act

IB Investigator's Brochure ICF Informed Consent Form

ICH International Conference on Harmonization

IDE Investigational Device Exemption

IEC Independent or Institutional Ethics Committee

IND Investigational New Drug
IRB Institutional Review Board
ISM Independent Safety Monitor

MedDRA © Medical Dictionary for Regulatory Activities

MOP Manual of Procedures

N Number (typically refers to participants)

NCI National Cancer Institute, NIH

NDA New Drug Application

NIAID National Institute of Allergy and Infectious Diseases, NIH

NIH National Institutes of Health

OHRP Office for Human Research Protections
OHSR Office for Human Subjects Research

PHI Protected Health Information

PI Principal Investigator
PK Pharmacokinetics
QA Quality Assurance
QC Quality Control

SAE Serious Adverse Event/Serious Adverse Experience

SMC Safety Monitoring Committee

# **List of Abbreviations**

SOP Standard Operating Procedure WHO World Health Organization

# **Protocol Summary**

Limit Protocol Summary to 2 pages. The summary may be presented in narrative or tabular format. See below:

Full Title	Include type of trial (e.g., dose-ranging, observational, double blind)
Short Title	
Clinical Trial Phase	I, II, III, or IV
IND Sponsor (if applicable)	Name of IND Sponsor (if applicable).
Conducted By	Name of Network or Program
Principal Investigator	Name of Lead Principal Investigator (Protocol Chair)
Sample Size	
Study Population	Include a brief description such as health status (e.g., healthy volunteers or HIV-positive), gender, age, etc.
Accrual Period	Length of time to completely enroll the study
Study Design	Provide an overview of the study design, including description of study type (e.g., double-masked, placebo-controlled, open label, dose-finding, parallel or crossover design, randomized), study arms, sample size and schedule of interventions (e.g., vaccine administration), if applicable.
Study Duration	State duration per participant. Provide the total length of time participants will be on study (intervention + follow-up)
Study Agent/Intervention Description	Include name, dose, duration frequency, and route of administration, if applicable
Primary Objective	Include primary outcome measures and method by which outcomes will be determined.

Secondary Objectives	Include secondary outcome measures and method by which outcomes will be determined.
Exploratory Objectives	(If applicable) Include exploratory outcome measure(s) that may ask separate research questions from the parent protocol.
Endpoints	

## Schematic of Study Design:

# Below are examples of schematics. Choose or create a schematic that is appropriate for a particular protocol.

Example #1: Table format: (e.g., dose escalation)

Cohort A	ARM 1	Sample Size	Intervention 1
	ARM 2	Sample Size	Intervention 2

Instructions for progressing to next phase (if applicable):

Cohort B	ARM 1	Sample Size	Intervention 1
	ARM 2	Sample Size	Intervention 2

Example #2: Flow diagram: Prior to Total N: Obtain informed consent. Screen subjects by criteria; obtain history document. **Enrollment** Randomize ₹<u>J</u> <u>J</u> ŢŢ N subjects N subjects N subjects Arm 3 Arm 1 Arm 2 Perform pregnancy test; collect blood for assays; Time Point or Administer Study Product/Intervention Study Visit 1 Time Point or Clinical and AE assessment Study Visit 2 Time Point or Clinical and AE assessment Study Visit 3 Time Point or Study Visit ... **Assessment of Final Study Outcome Measures** 

## 1. KEY ROLES

For questions regarding this protocol, contact (insert name of appropriate NIAID staff) Division/NIAID (insert contact information).

### A. Required Elements:

**Institutions**: Sponsor(s), Medical Monitor (if other than Sponsor), Study sites\*, Clinical laboratory (ies) and other medical or technical departments and/or institutions.

\*Alternatively, sites may be listed in a manual of procedures, if applicable.

Provide the following information for each organization or institution:

Institution Address

Contact Person Phone Number Fax Number E-mail

**Individuals**: **Sponsor**: *Individual authorized to sign the protocol and protocol amendments for the Sponsor and the Sponsor's medical expert for the trial* 

**Investigators**: Lead investigator(s) responsible for conducting the trial and the qualified physician who is responsible for all trial-site related medical decisions

Provide the following information for each individual:

Name, degree, title Institution

Address

Phone Number
Fax Number

E-mail

**B.** Optional Elements: (consider listing, for example):

Major International Collaborators, if not included as site

investigators

Protocol Data Manager Protocol Epidemiologist Protocol Pharmacologist

NIAID Clinical Trials Specialist

Pharmaceutical Company Representative(s)

Protocol Statistician(s)
Collaborating Investigators

Medical Monitor (Pharmaceutical Company)

NIAID Medical Monitor Independent Safety Monitor

Other individuals should be listed in a separate document (e.g., the Manual of Procedures) as a contact list.

# 2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 Background Information

#### Include:

- The name and description of the Study Agent(s)/Intervention(s)
- Discussion of important literature and data that are relevant to the trial and that provide background for the trial
- Applicable clinical, epidemiological or public health background or context of the study
- Importance of the study and any relevant treatment issues or controversies
- A focus on new information to explain the study in the context of a rapidly changing field
- Presentation of background in a manner that can be used in the background of a resultant manuscript
  - 2.1.1 Description of the Study Agent(s)/Intervention(s)
  - 2.1.2 Summary of Previous Pre-clinical Studies

This is a summary of findings from non-clinical studies that have potential clinical significance

- 2.1.3 Summary of Relevant Clinical Studies
- 2.1.4 Summary of Epidemiological Data

#### 2.2 Rationale

Include a description of and justification for the study and its design, including route of administration, dosage, dosage regimen, dosage duration, intervention periods, and selection of study population. Justify any aspects of the study not approved by regional control authorities (e.g., different dosing schedule, new combination of drugs, new drug formulation, new

population) Include a statement of the hypothesis and briefly summarize the natural history of the disorder being studied.

## 2.3 Potential Risks and Benefits

Include a discussion of known and potential risks and benefits, if any, to human subjects.

#### 2.3.1 Potential Risks

Discuss the reason why the value of the information to be gained outweighs the potential risks involved

#### 2.3.2 Potential Benefits

## 3. STUDY OBJECTIVES

A detailed description of the **primary**, **secondary**, **and exploratory** objectives of the study is included in this section. These typically include:

- Statement of purpose: e.g., to assess, to determine, to compare, to evaluate
- General purpose, e.g., efficacy, safety, immunogenicity, pharmacokinetics
- Specific purpose, e.g., dose-response, superiority to placebo
- Method of assessing how the objective is met, i.e., the study outcome measures

# 3.1 Primary Objective

The primary objective must match the one used in the Statistical Design section.

# 3.2 Secondary Objectives

May or may not be hypothesis-driven and may include more general, non-experimental objectives (e.g.: To develop a registry or to collect natural history data.)

# 3.3 Exploratory Objectives

## 4. STUDY DESIGN

# 4.1 Description of the Study Design

A description of the trial design should include:

 A description of the type/design of trial to be conducted (e.g., placebocontrolled, double-mask, parallel design, open-label, dose escalation, dose-ranging)

- Phase of the trial
- The number of study groups/arms
- Single or multi-center
- Healthy or sick population
- In-patient or out-patient
- Description of study groups/arms including sample size (include a table, if appropriate)
- Approximate time to complete study enrollment
- The expected duration of subject participation
- A description of the sequence and duration of all trial periods, including follow-up (specify individual participants vs. entire trial)
- Name of Study Agent(s)/Intervention(s)
- Changes in scheduling, such as dose escalations
- Any stratifications
- Methods for collecting data for assessment of study objectives
- A specific statement of the primary and secondary outcomes to be measured during the trial (must be consistent with Study Objectives, as stated in Section 3)
- Other protocol-specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)

# 4.2 Study Endpoints

## 4.2.1 Primary Endpoint

The primary measurement and endpoint used to determine primary efficacy should be clearly specified.

## 4.2.2 Secondary Endpoints

## 4.2.3 Exploratory Endpoints

#### 4.2.4 Substudy Endpoints

# 5. STUDY POPULATION

 The study population and inclusion/exclusion criteria should be clearly defined in this section of the protocol.

- The section should include a discussion of recruitment strategies specifically for achieving NIH gender/minority guidelines.
- If women, minorities and children will not be recruited, explain why not. Refer to: http://grants2.nih.gov/grants/funding/women\_min/women\_min.htm
- If the study intends to enroll children, pregnant women, prisoners, or other vulnerable populations, see applicable sections of 45 CFR 46: Subpart B Additional DHHS Protections Pertaining to Research, Development and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization (45 CFR 46.201-46.211); Subpart C Additional DHHS Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects (45 CFR 46.301-46.306); Subpart D Additional DHHS Protections in Children Involved as Subjects in Research (45 CFR 46.401-409).
- Indicate from where the study population will be drawn (e.g., in-patient hospital setting, out-patient clinics, student health service). Where appropriate (single center studies), include names of hospitals, clinics, etc.
- Provide the target/proposed sample size; include estimates for dropouts.
- Indicate timing of enrollment and randomization (if applicable) into study.

Note: The inclusion and exclusion criteria should provide a definition of participant characteristics required for study entry.

# 5.1 Description of the Study Population

## 5.1.1 Participant Inclusion Criteria

Provide a statement that participants must meet all of the inclusion criteria to participate in this study and then list each criterion.

Examples include the following: informed consent obtained and signed, age, presence or absence of a medical condition/disease, required laboratory result, understanding of study procedures, ability to comply with study procedures for the entire length of the study, requirements for agreement to avoid conception, etc. If men and women of reproductive capability will be enrolled, include details of allowable contraception methods for trial (e.g., licensed hormonal methods).

## 5.1.2 Participant Exclusion Criteria

Provide a statement that all participants meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

Examples include the following: medical condition or laboratory finding that precludes participation, recent (with time frame) febrile illness that precludes or delays participation, pregnancy or breastfeeding, characteristics of household or close contacts (e.g., household contacts who are immunocompromised), known allergic reactions to components of the study agent(s), treatment with another investigational drug (with time frame), history of drug/alcohol abuse, receipt of prohibited concomitant medications, etc.

#### 5.1.2.1 Co-enrollment Guidelines

Specify guidelines for co-enrollment. Describe any restrictions or opportunities concerning other studies in which the patient may enroll, while participating in this study.

## 5.2 Strategies for Recruitment and Retention

Identify strategies for participant recruitment and retention.

## 6. STUDY AGENT/INTERVENTIONS

Note: If multiple study agents are to be evaluated in the study, they should be listed in the following subsections for each product and the sections should be numbered accordingly. Describe placebo or control product within the following subsections, if required.

Also describe type of control with rationale for choice of control (e.g. placebo, no treatment, active drug, dose-response, historical). Discuss known or potential problems associated with the control group chosen in light of the specific disease and therapies being studied.

# 6.1 Study Agent Acquisition

## 6.1.1 STUDY DRUG # 1 (Primary Study Agent for this Trial

#### 6.1.1.1 Formulation, Packaging, and Labeling

Information in this section can usually be obtained from the Investigator's Brochure (IB) or the package insert. Make IB or package insert available to all investigators as part of the study's Manual of Procedures (MOP) or distributed separately, as appropriate. This section should include the name of the manufacturer of study agent(s) and/or placebo.

#### 6.1.1.2 Study Agent Storage and Stability

Describe product's storage needs. Include storage requirements and stability (temperature, humidity, security, container).

Provide additional information regarding stability and expiration time for studies in which multi-dose vials are entered (i.e., the seal is broken).

# 6.1.1.3 Preparation, Administration, and Dosage of Study Agent(s)/Intervention(s)

Include thawing, diluting, mixing, reconstitution/preparation instructions, as appropriate. List study agents, route, doses, duration, and frequency of administration in this section. Include any specific instructions or safety precautions for administration of study products or masking (blinding) of the product for the administrator. Include maximum hold time and conditions of product once thawed, mixed, diluted, reconstituted, etc.

### 6.1.1.4 Study Product Accountability Procedures

Provide plans for how the Study Agent(s)/Intervention(s) will be distributed including participation of a drug repository, frequency of product distribution, amount of product shipped, and plans for return of unused product.

#### 6.1.2 STUDY DRUG #2

- 6.1.2.1 Formulation, Packaging, and Labeling
- 6.1.2.2 Study Agent Storage and Stability
- 6.1.2.3 Preparation, Administration, and Dosage of Study Agent(s)/Intervention(s)
- 6.1.2.4 Study Product Accountability Procedures

# 6.2 Assessment of Participant Compliance with Study Agent(s)/Intervention(s)

Include plans for compliance assessment (e.g., questionnaires, direct observation, pill counts) in this section.

#### 6.3 Concomitant Medications and Procedures

List/describe permitted medications or drugs/interventions..

# 6.4 Precautionary and Prohibited Medications and Procedures

Refer to the most recent package insert or investigator's brochure to access additional current information on prohibited and precautionary medications.

#### 6.4.1 Prohibited Medications and Procedures

If applicable, list all medications/procedures that are NOT permitted on study. Include drugs from the exclusion criteria if they are also prohibited while the participant is on study.

## **6.4.2 Precautionary Medications and Procedures**

If applicable, list all medications/procedures for which there are precautions for concomitant use with the study products/interventions. Include instructions for dose modification, if appropriate.

# 6.5 Prophylactic Medications and Procedures

If applicable, list all medications and/or treatment that will be provided as prophylaxis on study.

## 6.6 Rescue Medications

If applicable, list all drugs and/or treatments that may be provided on study for "rescue therapy". Note: This section should be consistent with the medications restrictions in the inclusion/exclusion criteria.

## 7. STUDY PROCEDURES/EVALUATIONS

Information outlined in the Procedures/Evaluations section should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix B. A complete and detailed schedule of procedures/evaluations (ex. Appendix B) may be submitted in lieu of or in addition to this narrative description)

#### 7.1 Clinical Evaluations

List all clinical evaluations to be done during the protocol, and provide details/timelines at each visit of what are included and special instructions, if any.

#### Examples:

- Medical History (describe what is included for history, e.g., timeframe considerations, whether history will be obtained by interview or from medical records).
- Medications History (e.g., describe if a complete medications history is needed, or if only currently taken medications should be included; prescription medications only or also over-the-counter). Assessment of eligibility should include a review of permitted and prohibited medications.
- Physical Exam (list the vital signs and organ systems to be assessed); if appropriate, discuss what constitutes a targeted physical exam and at what visits it may occur. If an Adverse Event occurs, describe if a full physical exam should be done.

- Reactogenicity assessments (e.g., pain, tenderness; describe rating scale).
- Review of diary cards.
- Counseling procedures.
- Radiologic procedures (e.g., chest x-rays, DEXA scans, CT scans).

# 7.2 Laboratory Evaluations

# 7.2.1 Clinical and Research Laboratory Evaluations and Specimen Collection

List all protocol laboratory evaluations. Include specific test components and type of specimens needed for each test (e.g., plasma or serum). Specify laboratory methods (e.g., use consistent laboratory method throughout study) to provide for appropriate longitudinal and cross-comparison.

## Examples:

- Hematology: hemoglobin, hematocrit, white blood cells (WBC) with differential, platelet count
- Biochemistry: creatinine, total bilirubin, alananine aminotransferase (ALT), aspartate aminotransferase (AST), glucose (fasting/non-fasting)
- Urinalysis: dipstick urinalysis, including protein, blood and glucose; if dipstick is abnormal, complete urinalysis with microscopic is required.
- Pregnancy test usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.
- Biopsy specimens: tissue

#### Special Assays or Procedures

List special assays or procedures required to assess the study product (e.g., immunology assays, PK studies, photographs). For laboratory assays, include specific assays, estimated volume and type of specimen needed for each test. For procedures, provide special instructions or precautions. If more than one laboratory will be used, specify which assays or evaluations will be done by each laboratory.

### **Biohazard Containment**

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended

by the Centers for Disease Control and Prevention and the National Institutes of Health.

All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72. Also refer to individual carrier guidelines, e.g., Federal Express, Airborne Express, for specific instructions.

## 7.2.2 Specimen Preparation, Handling and Shipping

If the protocol involves any transport of materials that include infectious substances, diagnostic specimens, toxic chemicals, or hazardous materials, then prepare a plan for handling these shipments according to current regulations. Principal Investigators are responsible for knowing about and observing (and ensuring protocol collaborators also comply with) all the regulations for classification, packaging and labeling, permits or authorizations, and personnel training for shipment of biological and hazardous materials required for the conduct of the protocol. Failure to comply with federal and international regulations on shipment of biological or hazardous materials can result in refusal of the carrier to complete the shipment, fines, and/or jail. The following websites should be consulted for shipping regulations that may apply to the protocol:

- Department of Transportation. 49CFR171-180. Hazardous Materials Regulations. http://www.hazmat.dot.gov/rules.htm
- Public Health Service 42CFR72. Interstate Shipment of Etiologic Agents. 42CFR
  Part 72. Federal Register, Vol. 45, No. 141-Monday, July 21, 1980.
  <a href="http://www.cdc.gov/od/ohs/biosfty/shipregs.html">http://www.cdc.gov/od/ohs/biosfty/shipregs.html</a>
- Dangerous Goods Regulations. International Air Transport Association (IATA). <u>http://www.iata.org</u>
- Guidelines for the Safe Transport of Infectious Substances and Diagnostic Specimens. World Health Organization, 1997. http://www.who.int/emc/biosafety.html
- United States Postal Service. 39CFR111. Mailability of Etiologic Agents. Codified in the Domestic Mail Manual 124.38: Etiologic Agent Preparations. DMM Issue 55, January 10, 2000. <a href="http://www.access.gpo.gov/">http://www.access.gpo.gov/</a>
- Occupational Health and Safety Administration (OSHA). 29CFR1910.1030.
   Occupational Exposure to Blood borne Pathogens. <a href="http://www.osha.gov">http://www.osha.gov</a>

#### 7.2.2.1 Instructions for Specimen Storage

This section should include a discussion of long-term access and consent for future use of specimens, if applicable.

#### 7.2.2.2 Specimen Shipment

Refer to Appendix B for full schedule details of specimens and to Appendix C2 for specimen shipment details including labeling requirements.

### 7.3 Substudies

If a substudy is added to an ongoing parent study at a later time, a protocol amendment is required.

Definition: A substudy asks a separate research question from the parent protocol and does not overlap with the parent protocol's objectives, but uses all or a subset of study participants or specimens.

A concept sheet for a proposed substudy should be approved by the NIAID Project Officer/Program Officer prior to development of a full protocol for the substudy. Once the concept for a substudy is approved by the Program Officer, a decision will be made by NIAID, in conjunction with the Investigator as to whether the concept is appropriate as a substudy or should be a stand-alone study.

List with brief description:

- Description of the substudy and its objectives
- Impact on the main study
- Behavioral issues

## 8. STUDY SCHEDULE

Information outlined in the Study Schedule section should refer to and be consistent with the information in the Schedule of Procedures/Evaluations in Appendix B.

Allowable windows should be stated for all visits. To determine the appropriate windows, consider feasibility and relevance of the time point to study outcome measures (e.g., PK studies may allow little or no variation, with required time points measured in minutes or hours, whereas a 6-month follow-up visit might have a window of several weeks).

The schedule must include not only clinic visits but all contacts, e.g., telephone contacts.

# 8.1 Screening

Include only those evaluations necessary to assess whether a participant meets enrollment criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the timeframe prior to enrollment within which screening tests and evaluations must be done (e.g., within 28 days prior to enrollment). Refer to Section 7 Study Procedures/Evaluations for details of clinical evaluations and laboratory evaluations for screening.

This section must include instructions for obtaining signed informed consent.

## 8.2 Enrollment/Baseline

Discuss evaluations/procedures necessary to assess or confirm whether a participant still meets the eligibility criteria and may be enrolled, and those assessments that are required at baseline for later outcome measure comparison after study intervention (e.g., baseline signs and symptoms prior to vaccination). Discuss the sequence of events that should occur during enrollment and/or initial administration of study product. List any special conditions (e.g., results of the pregnancy test must be negative and available prior to administration of study product). List the procedures for administering the study product or intervention, and follow-up procedures after administration (e.g., assessment of vital signs, reactogenicity).

## 8.3 Follow-up

Include discussion of evaluations/procedures required to assess or confirm study outcome measures and study evaluations. Discuss the sequence of events that should occur during the visit, if applicable. Include, as applicable, counseling, review of reactogenicity, medications, assessment of adverse events, etc.

## 8.4 Final Study Visit

Define when the final study visit should occur and any special procedures/evaluations or instructions to the participant. Describe provisions for follow-up of ongoing adverse events/serious adverse events.

# 8.5 Early Termination Visit

Specify which of the evaluations required for the final study visit should be done at a termination visit if early termination occurs and if the participant is willing. Participants may withdraw voluntarily from participation in the study at any time. Participants may also withdraw voluntarily from receiving the study intervention for any reason. Clearly differentiate between what evaluations are to be done in each of these circumstances.

If voluntary withdrawal occurs, the participant should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the participant's condition becomes stable. Describe efforts to continue follow-up, especially for safety outcome measures.

# 8.6 Pregnancy Visit

The protocol should address the procedures to be followed if a participant becomes pregnant while on study. Indicate whether the participant will be allowed to continue to receive the Study Agent(s)/Intervention(s).

Provide any other guidance relevant to the study agent and pregnancy and/or breastfeeding.

#### 8.7 Unscheduled Visits

Describe procedures for unscheduled visits. Unscheduled visits may be necessary under a number of circumstances (e.g. the need for laboratory/clinical/safety evaluations.)

## 9. ASSESSMENT OF SAFETY

Reference safety parameters that are outcome measures

## 9.1 Specification of Safety Parameters

Include this section if safety is not a primary study outcome measure.

# 9.2 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a Study Agent(s)/Intervention(s) and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) Study Agent(s)/Intervention(s), whether or not related to the medicinal (investigational) Study Agent(s)/Intervention(s).

Provide a definition of expected vs. unexpected AEs, based on the risk profile of the Study Agent(s)/Intervention(s). This information is found on the CIB or package insert. For expected Events Related to Study Intervention: Provide explicit definitions of the type(s), grade(s), and duration(s) of adverse event(s) that will be considered treatment related.

(Note: for Vaccine Studies and Some Therapeutic Trials) Reactogenicity: In vaccine trials consider a definition of reactogenicity: Reactogenicity events are adverse events that are common and known to occur for the Study Agent(s)/Intervention(s) being studied and should be collected in a standard, systematic format using a graded scale based on functional assessment or magnitude of reaction. Typically, reactogenicity adverse events are solicited and collected on diary cards.

## 9.3 Definition of a Serious Adverse Event (SAE)

Serious Adverse Event (SAE): A Serious Adverse Event is defined as an AE meeting one of the following conditions:

- Death during the period of protocol defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

# 9.4 Methods and Timing for Assessing, Recording, and Analyzing, Managing Safety Parameters

This section should be based on the risk profile of the Study Agent(s)/Intervention(s). Include a review of relevant literature, which should be referenced. Add relevant websites, etc. from which the information could be drawn.

If a package insert is available, it should be used as the primary source of risk information. If the study agent is investigational, the IB should be the primary source of the risk information. In addition, literature searches can also provide relevant risk information. If the risk profile cannot be described from any of the above sources, the risk information discussion will result from the literature search and review.

# 9.4.1 Methods and Timing for Assessment

Describe the means of obtaining adverse event data. Describe which adverse events will be collected as solicited events and the format used to capture the solicited event (checklist, structured questioning, diary, etc), and any specific rating scale if one is to be used. Describe how unsolicited events will be captured. Describe the time period for adverse event collection.

### 9.4.1.1 AE/SAE Grading and Relationship Assignment

Assessment should include the intensity (severity) of the event, whether clinical or laboratory, and the relationship to Study Agent(s)/Intervention(s). (Collection of laboratory data should be limited to those laboratory parameters that are relevant to safety, study outcome measures and/or clinical outcome.)

Intensity will be assigned using a protocol defined grading system. The	'nе
Toxicity Tables (grading system) will define what values or clinical	
findings are considered abnormal. [Reference tables for	
laboratory/clinical events APPENDIX & APPENDIX ]	
(Selection of a toxicity table should be made in conjunction with NIAII	D.)

For events not included in the protocol defined grading system, include guidelines here for assessment.

#### **SAMPLE** Intensity (severity) Scale:

- **Grade 1 (Mild)**: events require minimal or no treatment and do not interfere with the patient's daily activities.
- Grade 2 (Moderate): events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Grade 3 (Severe): events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Grade 4 (Life threatening): Any adverse drug experience that
  places the patient or participant, in the view of the investigator, at
  immediate risk of death from the reaction as it occurred, i.e., it does
  not include a reaction that had it occurred in a more severe form,
  might have caused death.
- Grade 5 (Death)

Relationship Assessment of AEs/SAEs to the the Study Agent(s)/Intervention(s should be made by the principal investigator. (NOTE: Relationship assessment is not a factor in determining what is or is not reported in the study.) Adverse events may have their relationship to the Study Agent(s)/Intervention(s) assessed using the following terms: associated or not associated.

Other alternative relationship terms may be used (sample below).

SAMPLE Language

### <u>Definitely Related</u>

There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

### **Probably Related**

There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

#### Possibly Related

There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possible" soon after discovery, it can be flagged as requiring more information and later be upgraded to probable or certain as appropriate.

#### Unlikely

A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

### Not related

The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinicianExpected Events Related to Disease Process: Provide explicit definitions of the type(s), grade(s), and duration(s) of adverse event(s) that will be considered disease related.

## 9.4.2 Recording/Documentation

The documentation system for the protocol (Case Report Forms, electronic data capture systems, etc) should be clearly described in this section.

Complete description of all adverse events must be available in the source documents. All Adverse Events including local and systemic reactions not meeting the criteria for "serious adverse events" should be captured on the appropriate case report form or electronic data system. Information to be recorded, based on above assessment criteria, includes event description, time of onset, investigator assessment of severity, relationship to Study Agent(s)/Intervention(s), and time of resolution/stabilization of the event. All adverse events occurring while on study must be documented appropriately regardless of relationship. Define a timeframe for CRF completion and entry of the adverse event information into the database, as applicable.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not recorded as an AE. However, if the condition deteriorates at any time during the study it should be recorded and reported as an AE.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of the onset and duration of each episode.

Changes in the assessment of <u>relationship</u> to the Study Agent(s)/Interventions should also be clearly documented.

# 9.4.3 Analysis/Management

Describe the provisions for ensuring necessary medical or professional intervention for adverse events of the research. Include the plan to follow all adverse events to adequate resolution. Include plans and procedures, and the persons responsible for communicating to subjects information arising from the study (on harm or benefit, for example), or from other research on the same topic that could affect subjects' willingness to continue in the study.

# 9.5 Reporting Procedures

All clinical trials must have an AE/SAE reporting system in place.

Include details of the protocol-specific reporting procedures, the responsible individuals (e.g., the Investigator, the Medical Monitor, etc.), which case report forms should be completed, how and to whom (IRB, sponsor, DSMB etc) reports will be distributed, and what follow-up is

required. The specified time frames for reporting events should be in accordance with applicable regulations, NIAID requirements, any additional institutional requirements and in some cases, specific protocol requirements due to the unique nature of the study. (Consider the context of the trial and adjust reporting procedures appropriately for the study population and agent/intervention(s) being studied. Define the circumstances (for instance, severity grades >2 in which abnormal laboratory values will be reported as AEs/SAEs. Generally, in healthy people, a grade 3 or above abnormality is an SAE. In sick populations, define in terms of a change from baseline and disease progression.)

Include specific details of reporting procedures for:

- Adverse Events (AEs)
- Serious Adverse Events (SAEs) Grade 1-3
- Serious Adverse Events (SAEs): Grade 4 or higher
- Specify events that require reporting in an expedited time frame (e.g., abnormal laboratory values [Grade 3 or 4], HIV infection, pregnancy) to IND sponsor or other required entities.
- Social harms should they be likely to occur in the study on the basis of the study population, intervention, or as a result of the study participation.

# 9.5.1 Specific Serious Adverse Event Requirements

All serious adverse events will be:

- recorded on the appropriate serious adverse event case report form
- followed through resolution by a study physician
- reviewed by a study physician

Any AE that meets the division's or protocol-specific expedited (or serious) adverse event reporting criteria must be submitted to the NIAID's pharmacovigilance contractor, at the following address, using the appropriate form (if applicable):

Medical Affairs/Pharmacovigilance <Insert Clinical Research Organization Name> <Insert CRO Address and Contact Information> SAE Fax line: <Insert SAE FAX #>

Questions about expedited (SAE) SAE reporting can be referred to the Expedited/SAE Hotline (available 24 hours a day/7 days a week) at <Insert SAE Hotline Telephone #>

Contact the NIAID Division or Branch for details on Expedited Adverse Event or SAE reporting.

The study clinician will complete an Expedited or Serious Adverse Event Form within the following timelines:

All deaths and immediately life threatening events, whether related or unrelated, will be recorded on the Expedited or Serious Adverse Event Form and faxed/electronically communicated within 24 hours of site awareness.

Adverse events other than death and immediately life threatening events, that meet expedited reporting criteria, regardless of relationship, will be faxed/electronically communicated by the site within 72 hours of becoming aware of the event.

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

All reportable AEs will be followed until satisfactory resolution or until the Principal Investigator or Subinvestigator deems the event to be chronic or the participant to be stable.

#### REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER NIAID-SPONSORED IND

Following notification from the investigator, NIAID, the IND sponsor, will report events that are both serious and unexpected and that are associated with Study Agent(s)/Intervention(s) to the FDA and other applicable health authorities within the required timelines as specified in 21 CFR 312.32: fatal and life threatening events within 7 calendar days (by phone /fax/electronic communication) and all other serious adverse events in writing within 15 calendar days. All serious events designed as "not associated" to Study Agent(s)/Intervention(s), will be reported to the FDA at least annually in a summary format.

# 9.6 Reporting of Pregnancy

Report within the timeframe specified by the NIAD Division or Branch. State the study's pregnancy-related policy and procedure. Include appropriate mechanisms for reporting to sponsor, study leadership, IRB, and regulatory agencies. Provide appropriate modifications to study procedures (e.g., discontinuation of Study Agent(s)/Intervention(s) while continuing safety follow-up, following pregnant women to pregnancy outcome).

The following is a scenario to consider in the event of pregnancy while on study: Pregnant women are not eligible to participate in the study. Women are counseled regarding prevention of pregnancy and encouraged to make every effort to avoid pregnancy during study participation. If a study participant becomes pregnant during study participation, [no further doses of study agent(s) are given or study intervention is discontinued]. Depending upon the nature of the study, the pregnancy itself may not need to be recorded as an adverse event. The basic information about the pregnancy is recorded on the "Pregnancy"

case report form. If there are complications during the pregnancy, the complications are recorded as adverse events in the usual way. The participant is asked to report outcome of the pregnancy. If there is a congenital anomaly in the infant, this is recorded as a serious adverse event (SAE) in the data forms for the mother (i.e., the study participant)."

Also consider language if a woman becomes pregnant while on study and is able to continue receiving the study agent/intervention.

# 9.7 Type and Duration of the Follow-up of Participants after Adverse Events

Describe how adverse events, reportable to the IND sponsor, will be followed until resolved or considered stable. Specify procedures for reporting and follow-up of AEs that are consistent with the Schedule of Procedures/Evaluations. Include duration of follow-up period after the appearance of AEs (e.g., one week, two months).

# 9.8 Modification of Study Agent(s)/Intervention(s) for a Participant

Note: Different types of products will require different instructions for this section. If the study utilizes multiple study agents, clearly indicate toxicity management for each study agent.

Figure 1: Below is an example to describe toxicity for a commonly occurring toxicity related to liver function tests. This type of figure can be adapted to describe various steps of toxicity management.

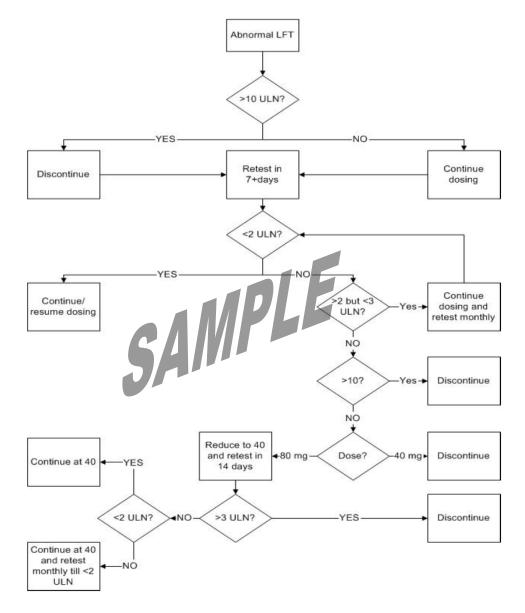


Figure 1: Liver function test monitoring

## 9.8.1 Dose / Schedule Modifications for a Participant

Clearly explain instructions for modification of dose due to toxicity or any other potential reason. Address dose modifications for specific abnormal laboratory values of concern or other adverse events that are known to be associated with the planned intervention regimen.

## 9.9 Halting Rules for the Protocol

Describe safety findings that would temporarily suspend enrollment and/or study agent/ intervention(s) until a safety review is convened (either routine or ad hoc). The objective of which is a decision as to whether the study agent/intervention (for an individual or study cohort) should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed. Suspension of enrollment (for a particular group or for the entire study) is another potential outcome of a safety review.

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events.

Subsequent review of serious, unexpected and related adverse events by the Medical Monitor, DSMB, ethics review committee or IRB, the sponsor(s), the FDA, and other regulatory authorities may also result in suspension of further trial interventions/administration of study agent at a site. The FDA, other regulatory authorities, and the study sponsor(s) retain the authority to suspend additional enrollment and Study Agent(s)/Intervention(s) administration for the entire study as applicable.

## 9.10 Stopping Rules for an Individual Participant/Cohort

Criteria for Discontinuation of Study Agent(s)/Intervention(s) for Withdrawal of a Participant (or a Cohort)

List possible reasons for discontinuation of the study agent(s)/intervention(s) (for an individual/cohort) in this section, e.g., development of laboratory toxicities, study closure due to DSMB review, discretion of NIAID/or IND holder.

It may be appropriate to provide distinct discontinuation criteria for participants and cohorts. If so, both sets of criteria should be listed separately and the distinction between the two must be stated clearly.

Sample language: A study participant will be discontinued from further Study Agent(s)/Intervention(s) if:

 Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

Development of any exclusion criteria may be cause for discontinuation.

Note that participant will continue to be followed with participant's permission if Study Agent(s)/Intervention(s) is discontinued. Discuss resulting modifications to the schedule and duration of continued follow-up.

## 9.11 Premature Withdrawal of a Participant

Describe the follow-up for subjects withdrawn from study, include the type and timing of the data to be collected for withdrawn subjects. The protocol should clearly state that voluntary withdrawal is always an option.

# 9.12 Replacement of a Participant Who Discontinues Study Treatment

Describe whether and how subjects are to be replaced.

## 10. CLINICAL MONITORING STRUCTURE

This section will describe the study monitoring to be conducted to ensure that the safety and conduct of the study complies with 45 CFR 46, GCP and ICH Guidelines, NIAID and other sponsor collaborator's guidelines, as appropriate.

## 10.1 Site Monitoring Plan

Site monitoring for safety is conducted to ensure the human subject protection, study procedures, laboratory, Study Agent(s)/Intervention(s) administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines. This section will give a general description of how site monitoring will be conducted. A separate monitoring plan document should be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

Preference is given to a separate monitoring plan or in the Manual of Procedures, to be agreed upon with the NIAID review group or Division, which will describe protocol specific items to be monitored. The monitoring plan must include the number of participant charts to be reviewed, which/what proportion of data fields and what will be monitored, and who will be responsible for conducting the monitoring visits, and who will be responsible for ensuring that monitoring findings are addressed.

# 10.2 Safety Monitoring Plan

NIAID and the investigators will jointly decide on a safety monitoring plan for each trial. When potential risk to participants is more than minimal, NIAID strongly recommends independent safety monitoring for clinical trials of investigational drugs, devices, or biologics. Phase IV clinical trials of licensed products, and clinical research of any type involving more than minimal risk to volunteers must also have a safety monitoring plan. Independent safety monitoring can take a variety of forms; phase II, III, and IV clinical trials generally require an independent Data and Safety Monitoring Board (DSMB). NIH policy for data and safety monitoring boards may be found at the following internet web address: <a href="http://grants.nih.gov/grants/quide/notice-">http://grants.nih.gov/grants/quide/notice-</a>

<u>files/not98-084.html</u> and <u>http://grants2.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html</u>.

NIH policy requires each IC to oversee and monitor clinical trials; some monitoring requirements may vary by NIAID division.

#### 10.2.1 Safety Review Plan by the DSMB / SMC

#### 11. STATISTICAL CONSIDERATIONS

This section should describe the statistical tests and analysis plans for the protocol.

## 11.1 Overview and Study Objectives

Succinctly restate the scientific rationale for the study and the primary and most important secondary objectives from Section 3, to motivate choice of study population, outcome measures, hypotheses and design.

## 11.2 Study Population

Give a very concise restatement of the eligibility criteria, e.g., vaccinia-naïve healthy volunteers between the ages of 18 and 65.

Describe any control groups (i.e., active or placebo control groups, concurrent or historical controls, etc.) and a synopsis of the rationale for choosing them (i.e., including risk/benefit or other ethical factors).

# 11.3 Description of the Analyses

State the proposed formal design of the study (e.g., two-period crossover, two-by-three factorial parallel group, or case-control). If the design or interventions are complex, a schema may be included.

#### 11.4 Measures to Minimize Bias

#### **Enrollment/ Randomization/ Masking Procedures**

This section contains a description of enrollment procedures and randomization (if applicable to the study design) and enrollment procedures. It should include a description or a table that describes how study participants will be assigned to study groups, without being so specific that masking or randomization might be compromised (e.g., the ratio between intervention and placebo groups may be stated but the randomization block sizes should not). A discussion of replacement of participants who discontinue early, if allowed, should be included in this section.

Plans for the maintenance of trial randomization codes and maintaining appropriate masking for the study should be discussed. The timing and procedures for planned and unplanned breaking

of randomization codes should be included. Include a statement regarding when unmasking may occur and who may unmask.

Review strategies to avoid bias, such as randomization and masking methods, or decrease variability, such as centralized laboratory assessments. DO NOT include details that might compromise these strategies, such as the size of randomized blocks.

# 11.5 Appropriate Methods and Timing for Analyzing Outcome Measures.

An outcome measure is "an observation variable recorded for [participants] in the trial at one or more time points after enrollment for the purpose of assessing the effects of the study treatments" (Meinert 1986). Outcome measures should be prioritized. Generally, there should be just one primary variable, with evidence that it will provide a clinically relevant, valid and reliable measure of the primary objective (e.g., laboratory procedures, safety assays).

Give succinct but precise definitions of the outcome measures used to measure the primary and key secondary outcomes stated in the study objectives, including the study visits at which the samples will be obtained and the specific laboratory tests to be used.

Secondary outcome measures should be included, whether they add information about the primary objective or address secondary objectives. Discuss their importance and role in the analysis and interpretation of study results.

Discuss how the outcome measures will be measured and transformed, if relevant, before analysis (e.g., is the primary variable binary, categorical, or continuous? Will a series of measurements within a participant be summarized, such as by calculating the area under the curve? For survival outcome measures, what are the competing risks and censoring variables?).

# 11.6 Study Hypotheses

State the formal, testable, null and alternate hypotheses for primary and key secondary objectives, specifying the type of comparison (e.g., superiority, equivalence or non-inferiority, dose-response).

# 11.7 Sample Size Considerations

Provide all information needed to validate your calculations, and also to judge the feasibility of enrolling and following the necessary numbers of participants.

In particular, specify all of the following:

- Outcome measure used for calculations (almost always the primary variable)
- Test statistic

- Null and alternate hypotheses
- Type I error rate
- Type II error rate
- Assumed event rate for dichotomous outcome (or mean or variance of continuous outcome) for each study arm, justified and referenced by historical data as much as possible
- Assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc. also justified
- Approach to handling withdrawals and protocol violations, i.e., whether "intent to treat"
- Statistical method used to calculate the sample size, with a reference for it and for any software utilized
- Method for adjusting calculations for planned interim analyses, if any
- Present calculations from a suitable range of assumptions to gauge the robustness of the proposed sample size.

Discuss whether the sample size also provides sufficient power for addressing secondary objectives, or for secondary analyses in key subgroup populations.

#### 11.8 Maintenance of Trial Treatment Randomization Codes

# 11.9 Participant Enrollment and Follow-Up

Summarize the total number of enrolled participants and the total duration of accrual and of final follow-up, being specific about the number of clinical sites and their enrollment and retention capabilities. Also be explicit about distinct stages in enrollment, if applicable.

# 11.10 Planned Interim Analyses (if applicable)

If interim analyses will be reviewed by Data and Safety Monitoring Board (DSMB) or a similar committee, describe the frequency of review (e.g., on a quarterly basis).

Describe the types of statistical interim analyses and stopping guidelines (if any) that are proposed, including their timing.

Within the two sections below, the criteria used to determine decisions should be pre-specified to the extent possible.

# 11.11 Safety Review

Provide details of the proposed rules for halting study enrollment or Study Agent(s)/Intervention(s) administration of study product for safety, including whether they

pertain to the entire study, specific study arms or participant subgroups, or other components of the study.

State the safety outcome measures that will be monitored, the frequency of monitoring, and the specific definitions of proposed stopping guidelines.

If statistical rules will be used to halt enrollment into all or a portion of the study, describe the statistical techniques and their operating characteristics, e.g., the probability of stopping under different safety event rates and the associated number of participants that would be enrolled.

# 11.12 Immunogenicity or Efficacy Review

Provide the information for immunogenicity or efficacy outcome measures. Also discuss the impact of the interim monitoring plan on final efficacy analyses, particularly on Type I error.

If formal interim analyses will be performed, provide unambiguous and complete instructions so that an independent statistician could perform the analyses.

## 11.13 Final Analysis Plan

This section can be used to elaborate on primary analyses that underlie the sample size calculation and to describe secondary analyses for the primary or secondary objectives. Even more details can be provided in a separate statistical analysis plan written later, but prior to performing any analyses.

Plans must clearly identify the analyses cohorts (e.g., "Per Protocol" or "Intent to Treat", as well as subsets of interest) and methods to account for missing, unused or spurious data.

# 12. QUALITY CONTROL AND QUALITY ASSURANCE

This section will briefly indicate the plans for local quality control (QC). Each site should have standard operating procedures (SOPs) for quality management. Data will be evaluated for compliance with protocol and accuracy in relation to source documents. The study will be conducted in accordance with procedures identified in the protocol. The types of materials to be reviewed, who is responsible, and the schedule for reviews may be specified or referenced in other documents. Types and mechanisms of training of staff for the study should be specified.

Specify whether the study will be conducted at multiple centers or a single center.

SOPs must be used at all clinical and laboratory sites. Regular monitoring and an independent audit must be performed according to GCP/ICH (e.g., data monitoring).

Briefly describe methods (e.g., site monitoring) for assuring protocol compliance, ethical standards, regulatory compliance and data quality.

#### Example text:

"Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Reports will be submitted to NIAID on monitoring activities.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

The Data Coordinating Center (DCC) will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution."

# 13. ETHICS/PROTECTION OF HUMAN SUBJECTS

This section should include a description of the ethical considerations and context for the conduct of the trial.

#### 13.1 Declaration of Helsinki

Include this section if applicable.

If the study is conducted at international sites, include a statement about compliance with the Declaration of Helsinki.

#### Example text:

"The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines, whichever affords the greater protection to the subject."

#### 13.2 Institutional Review Board/Ethics Committee

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate ethics review committee or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are placed into use. In both the United States and in other countries, only institutions holding a current U. S. Federal-Wide Assurance issued by the Office

for Human Research Protections (OHRP) may participate. Refer to: <a href="http://ohrp.osophs.dhhs.gov">http://ohrp.osophs.dhhs.gov</a>.

#### 13.3 Informed Consent Process

Describe the procedures for obtaining and documenting informed consent of study participants. Make provisions for special populations, e.g., non-English speakers, children, illiterate or non-writing individuals, vulnerable populations.

Informed consent is required for all subjects participating in an NIAID-sponsored study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/Independent Ethics Committee's written approval/favorable opinion of the written informed consent form(s) and any other written information to be provided to the participants.

Identify different consent forms that are needed for the study (e.g., screening, study participation, HIV screening, future use specimens, plasmapheresis, assent form for minors.)

#### Example text:

"Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants and their families. Consent forms describing in detail the Study Agent(s)/Intervention(s) study procedures and risks are given to the participant and written documentation of informed consent is required prior to starting study agent/intervention. Consent forms will be IRB approved and the participant will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the participant and answer any questions that may arise. The participants will sign the informed consent document prior to any procedures being done specifically for the study. The participants should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study."

Provide each institution with a sample consent form for subject participation. The consent form should be separate from the protocol document.

#### 13.3.1 Assent or Informed Consent Process (in Case of a Minor)

When a study includes participants who may be enrolled in the trial only with the consent of the participant's legally acceptable representative (e.g., minors or participants with severe dementia), the participant should be informed about the trial to the extent compatible with the participant's understanding. If capable, the participant should assent and sign and personally date the written consent form. A separate IRB-approved assent form, describing (in simplified terms) the details of the Study Agent(s)/Intervention(s), study procedures and risks may be used. Assent forms do not substitute for the consent form signed by the participant's legally acceptable representative.

# 13.4 Exclusion of Women, Minorities, and Children (Special Populations)

If the study intends to exclude any special populations, justify the exclusion of women, minorities or children in the context of the study design.

# 13.5 Participant Confidentiality

Include procedures for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

# 13.6 Study Discontinuation

In the event that the study is discontinued, provide a plan for the following:

- Describe procedures for participants to continue therapy, if appropriate.
- Crossover to study agent for placebo recipients at the completion of the study.

# 14. DATA HANDLING AND RECORD KEEPING

Include instructions for special data handling or record keeping procedures required for maintaining participant confidentiality, any special data security requirements, and record retention per the sponsor's requirements in this section.

Briefly describe steps to be taken to assure that the data collected are accurate, consistent, complete and reliable and in accordance with ICH GCP guidelines. The description should include reference to source documentation, case report forms, instructions for completing forms, data handling procedures, and procedures for data monitoring. Details may be provided in a Manual of Procedures (MOP), User's Guide or other citable reference document.

# 14.1 Data Management Responsibilities

Describe responsibilities for data handling and record keeping as they specifically relate to the sponsor, clinical site, laboratory, and data coordinating center. Information should include the role in data collection, review of data, trial materials, and reports, as well as retention of source documents, files, and records. Describe coding dictionaries to be used and reconciliation processes (if applicable). At the end of the study, a copy of all datasets will be provided to NIAID. Describe who will send a copy of all datasets to NIAID electronically.

All source documents and laboratory reports must be reviewed by the clinical team and data entry staff, who will ensure that they are accurate and complete. Adverse Events must be graded, assessed for severity and causality and reviewed by the site Principal Investigator or designee.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

If data are to be generated in one location and transferred to another group, describe the responsibilities of each party.

Indicate the roles of each party with regard to interpretation of data, plans for analysis, review of tables and listings, and plans for reporting.

# 14.2 Data Capture Methods

Identification of Direct CRF Input Data and Other Source Data

Provide details regarding the type of data capture that will be used for the study. Specify whether it will be paper or electronic, distributed or central, batched or ongoing processing, and any related requirements. Indicate expectations for time for submission of CRFs.

# 14.3 Types of Data

Indicate the types of data that will be collected, such as safety, laboratory (clinical, immunology, pharmacokinetic, other study specific), and outcome measure data (e.g., reactogenicity). Specify if safety data are collected in a separate database.

#### 14.4 Source documents and Access to Source Data/Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory and institutional requirements for the protection of confidentiality of participants. Describe who will have access to records. As part of participating in a NIAID-sponsored, NIAID-affiliated or manufacturer-sponsored study, each site will permit authorized representatives of the sponsor(s), NIAID, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

# 14.5 Timing/Reports

Indicate the schedule for data review and reports, how outcome measure data are collected and monitored, data for stopping rules, and reports for DSMB. Specify whether reviews or reports are ongoing, interim, or periodic. Identify plans for data analysis and interim and final study reports, steps for freezing the data prior to analysis, and precautions related to masked data. Indicate whether and when coding is to occur.

# 14.6 Study Records Retention

Specify the length of time for the investigator to maintain all records pertaining to this study (e.g., a minimum of two years following the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the Study Agent(s)/Intervention(s). Indicate whether permission is required (and from whom) prior to destruction of records. If the trial is under IND, records should not be destroyed without the IND sponsor's agreement. Pharmaceutical companies who supply unregulated products should be consulted.

Study Agent(s)/Intervention(s) records may be addressed here if not addressed elsewhere in the protocol.

#### 14.7 Protocol Deviations

Plans for detecting, reviewing and reporting deviations from the protocol should be described. A statement may be included to indicate that deviations are not allowed, unless a statement is included in investigator agreement. Provisions for acknowledgement of deviations can be described.

The following language may be used in the protocol:

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with Good Clinical Practice (GCP ICH E6) Sections:

Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3 Quality Assurance and Quality Control, section 5.1.1 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations according to the guidelines of the IND sponsor, if applicable.

Protocol deviations must be sent to the local IRB/IEC per their guidelines. The site Pl/study staff is responsible for knowing and adhering to their IRB requirements.

#### 15. PUBLICATION POLICY

Publication of the results of this trial will be governed by NIAID publication policies. Any presentation, abstract, or manuscript will be made available for review by the NIAID supporters prior to submission.

Any NIAID Division requirements should be referenced here.

In the case of collaborative studies with co-sponsoring agencies or other clinical trial groups, any letter of agreement must note which Standard Operating Procedure for publication of research findings is used.

#### Additional Considerations for the above section:

If appropriate, the publication policy may be described in the study Manual of Procedures (MOP). The publication and authorship policies should be determined and clearly outlined in this section. Refer to contract or clinical trials agreements. Policies regarding substudies should be outlined in this section.

The following text may used in the protocol:

Following completion of the study, the investigator may publish the results of this research in a scientific journal. The International Committee of Medical Journal Editors (ICMJE) member journals has adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry such as <u>ClinicalTrials.gov</u>, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. It is the responsibility of the NIAID Division or Branch to register this trial in an acceptable registry. Any clinical trial starting enrollment after 01 July 2005 must be registered either on or before the onset of patient enrollment. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by 13 September 2005 before considering the results of the trial for publication.

The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (eg, Phase 1 trials), would be exempt from this policy.

# **Appendix A1: Site Roster**

#### Example of Site Roster

If a protocol involves multi-centers, each site should have a site specific roster including key site staff as well as NIAID and Data Center (if used) contacts. Each of these rosters may then be placed in a Manual of Operations for access to all site staff.

[List participating clinical centers and any clinical laboratories being used as central laboratories for the study.] Others could include: Biostatistician, Data Manager, other disciplines, ie Virologist, Neurologist, etc.

SITE INVESTIGATOR-PRINCIPAL	SITE INVESTIGATOR-ASSOCIATE	NIAID MEDICAL MONITOR
[Nama]	[Amol/]	[Nama]

[Name] [Name] [Name] [Title] [Title] [Title] [Institution] [Institution] [Institution] [Address] [Address] [Address] [City/State/Zip] [City/State/Zip] [City/State/Zip] Phone: Phone: Phone: Fax: Fax: Fax: Email: Email: Email:

#### NIAID PROGRAM OFFICER PROJECT MANAGER LABORATORY STUDY CONTACT

[Name] [Name] [Name] [Title] [Title] [Title] [Institution] [Institution] [Institution] [Address] [Address] [Address] [City/State/Zip] [City/State/Zip] [City/State/Zip] Phone: Phone: Phone: Fax: Fax: Fax: Email: Email: Email:

Site Pharmacist
Site Study Coordinator
Data Coordinating Center Contact (example, data manager, biostatistician)

[Name] [Name] [Title] [Title] [Name] [Institution] [Institution] [Title] [Address] [Address] [Institution] [City/State/Zip] [City/State/Zip] [Address] [City/State/Zip] Phone: Phone: Fax: Phone: Fax: Fax:

EMAIL: EMAIL: FAX. EMAIL:

# **Appendix A2: Study Contacts Roster**

#### **Example of Study Contacts Roster**

The purpose of the study contacts sheet is to provide a centralized list of the key disciplines involved in the study in order to facilitate centralized communication. Depending on the structure of the study, the data center is often responsible for filtering all questions to the appropriate contacts and then disseminating the information to the appropriate person(s). In the event another system of communication is used, a detailed study contacts sheet is essential.

DRUG COMPANY REPRESENTATIVE (IF INVOLVED)

#### PRINCIPAL INVESTIGATOR (PROTOCOL CHAIR)

# [Name] [Title] [Institution] [Address] [City/State/Zip] Phone: Fax: Email:

#### **NIAID MEDICAL MONITOR**

[	Name]
[	Title]
[	Institution]
[	Address]
[	City/State/Zip]
F	Phone:
F	ax:
E	Email:

#### NIAID PROGRAM OFFICER

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

[Name]

[Address]

Phone:

Fax:

Email:

[City/State/Zip]

[Title] [Institution]

#### NIAID PROJECT MANAGER

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

#### NIAID Study Pharmacist

[Name] [Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:

EMAIL:

#### BIOSTATICIAN

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:

EMAIL:

#### DATA COORDINATING CENTER CONTACT

LABORATORY MAIN STUDY CONTACT

L	
1]	Name]
[	Γitle]
[]	nstitution]
[/	Address]
[(	City/State/Zip]
Ρ	hone:
F	ax:
_	
	MAIL:

#### DATA COORDINATING CENTER DATA MANAGER

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:

#### Fax: Email:

# VIROLOGIST, NEUROLOGIST, OR OTHER REQUIRED DISCIPLINES

[Name]
[Title]
[Institution]
[Address]
[City/State/Zip]
Phone:
Fax:

Email:

#### Additional Participating Clinical Sites-IContact Namel

[Contact Name]
[Title]
[Contact Institution]
[Address]
[City/State/Zip]
Phone:
Fax:
Email:

<sup>\*\*\*</sup>This may be listed on a separate page



# Appendix B: Schedule of Procedures/Evaluations

			Follow-Up Schedule						
Procedures		Screening	Baseline	Time Point or Study Visit 1	Time Point or Study Visit 2	Time Point or Study Visit 3	Time Point or Study Visit 4,	Study Completion	Premature Discontinuation
Signed Cons	ent Form	Х	Х						
Assessment	of Eligibility Criteria	Х	Х						
Review of Mo	edical History	Х	Х						
Review of Co Medications	oncomitant	Х	Х	Х	Х	Х	Х	Х	Х
Study Interve	ention		Х						
<u>_</u> _	Complete	Х						Χ	Х
Physical Exam	Symptom- Directed		Х	(X)	(X)	(X)	(X)		
ш.	Vital Signs		(X)	(X)	(X)	(X)	(X)		
Assessment	of Adverse Events			(X)	(X)	(X)	(X)	Χ	Χ
al ory	Chemistry	Х	Х	(X)	(X)	(X)	(X)	Χ	Χ
Clinical Laboratory	Hematology	Х	Х	(X)	(X)	(X)	(X)	Х	Х
	Urinalysis	Х	Х	(X)	(X)	(X)	(X)	Х	Х
Research Laboratory	Immunology mL whole blood		Х		(X)		(X)	Х	Х
Other			(X)		(X)		(X)	(X)	(X)

#### (X) – As indicated/appropriate.

Provide a list of tests to be done, e.g.:

Hematology – Hemoglobin, hematocrit, WBC and differential count, platelet count

Biochemistry – Sodium, potassium, chloride, urea, creatinine, glucose, uric acid, bicarbonate, amylase, lipase, albumin, total bilirubin, cholesterol, triglycerides, and CPK, as appropriate for the study. Note that this list is an example; specify list of tests applicable for the protocol.

Urinalysis - Protein and glucose, as appropriate for the study

Immunology – Specify specimen types for non-standard laboratory assays

Other – Other procedures that are done to evaluate outcome measures (e.g., photographs, X-rays)

Study Intervention - Modify as appropriate if intervention is administered more than once throughout the study

Specify time points for follow-up in days, weeks, or months, as appropriate for protocol.

At baseline, all procedures should be done before study intervention.

Indicate volume of blood if frequent or large phlebotomies are part of the protocol over two months.

# Appendix C1: Lab Processing Flow sheet (this can be modified for each protocol) Example of Lab Processing Chart for NIAID Protocol Assays

Date created or revised

Version #

Protocol #

	Handling- All spec	cimens must be logged into the specimen manage		l aliquots must be entered into the storage module and		
Visit	Study or Substudy #/ Patient Subset	olumes must be accurate and the # of aliquots er  Primary Spec. Collection and Handling	Tests	Processing		
Blank template Enter VID and time points (pre dose, 1hr, etc.)	Enter protocol #, step, arm, Sub-study #	Enter blood volume, tube additive- if anticoagulant, then write "Invert 10-15 times gently.", where to send for processing, temperature (ambient, on chipped ice), time limitation (for processing w/in 1 hour) Complete CRF # Submit CRF #	Full name of test then abbreviation Test Code:	None or Spin speeds, time of spin, temp. of spin, aliquots and volume, special processing (within x time of collection, refer to Appendix or Protocol Specific Information Sheet/MOP) where to ship(lab code, not whole address, ), when to ship (monthly, real-time, batch until week x) spec. code:		
Adult blood o	collection limit is 4	OR NIAID PROTOCOLS (Adult/Pediatric) I50mL every 56 days (8 weeks) is				
		ETY LABS (Local laboratory requirements may dine specific needs of the protocol.	iffer and supercede su	uggested specimen collection and handling) Each of		
	5mL SST or red top tube (no additive) - Send $\alpha$ fetoprotein None to local clinical lab ambient.					
		Serum (from 10mL SST or red top tube (no additive)) or urine (1mL) - Send to local clinical lab ambient.  Complete CRF #	β HCG (pregnancy test) (urine test must have a sensitivity of 25-50mIU/mL	None		
		No extra blood needed. Use 10mLSST tube or red top tube (no additive). Send to local clinical lab ambient.  Complete CRF #	Albumin	None		
		Tonsil biopsy +/or excisional lymph node biopsy (non-inguinal) - Send to local Pathology lab.  Complete CRF #	Biopsy examination	Process immediately in operating room, 50-75% of biopsy to be cut into 2mm slices in aluminum foil cups covered in OCT, ship to A single cell suspension( from lymph node biopsies only)of 5-40x10 <sup>6</sup> cells will be teased from the biopsy: send		

All specimens will be collected per Section 6.0, Schedule of Evaluations. Collection requirements are below. Processing details are located in the relevant appendix listed below. All specimens generated from this protocol must be labeled, stored and shipped according to the specific laboratory and Data Management System guidelines for the protocol unless otherwise specified.

TABLE

Assay/Procedure	Tube Type or Specimen Type and Quantity	Derivative	Processing Instructions	Aliquots/Storage	Shipping Address and Frequency
(Specify the assay name, use the same name as in Section	(Specify tube type, size,	(e.g. plasma,	(Specify where specific	(Specify the number and	
6.0)	additive required for blood draw (or indicate specimen	PBMCs, serum, etc.)	instructions are (e.g., PSIS) or if sent to a local	volume of aliquots and any instructions for	(Use shipping
0.0)	type and amount, e.g. lymph node tissue or CSF)	serum, etc.)	lab for processing)	freezing/storage on site)	links where appropriate)
VIROLOGY					
IMMUNOLOGY					
METABOLIC					
PHARMACOLOGY					

### Appendix D: Optional Supplements/Appendices

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports. These materials may be included as part of the protocol.)

#### Appendices may include:

- Schedule of Events
- Substudies
- Biosafety Precautions
- Repository Instructions
- Toxicity Grading Scales
- Laboratory Handling
- Investigator Brochure

Optional accompanying documents may include:

- Conflict of Interest Statement
- Financial Disclosure
- Sample Consent Form(s)
- Site and Safety Monitoring Plans
- Monitoring Plan
- CRF copies
- Manual of Procedures
- Package Inserts

Note: Other materials that may need to be submitted to the IRB include:

**Advertisements** 

Study Questionnaires

CRF copies

Patient Education Materials